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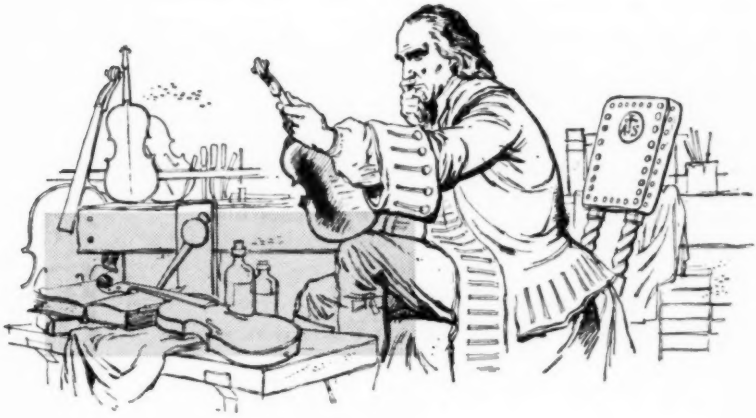

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EDITORIAL

PURE STREAMS OR OPEN SEWERS?

AMERICA is noted for the rate at which she has dissipated her natural resources and it is only in recent years that the cries of the conservationist were other than "a voice in the wilderness." Most people today sense the imperative need of forest and soil conservation and the war's heavy drain on our petroleum and mineral reserves have brought about some concern over these important commodities. Few indeed consider water as a limited natural resource but yet a critical situation is rapidly developing and unless it receives early attention serious consequences will develop.

Two factors are largely responsible for the growing water crisis. The first of these is the insatiable appetite for water possessed by our industrial and agricultural developments. The second is the almost criminal fashion in which we pollute our streams and rivers. The latter by destroying the essential purity of a water source eliminates its use and places an even greater drain on other sources of supply. This vicious circle has continued with an ever-increasing tempo until some areas are facing a situation that demands immediate action.

The need for water by certain industries is unbelievably large. The canning industry, which grows larger each day, is an example. Three gallons of water are used in packing a No. 2 can of asparagus, 7 gallons for a can of spinach and 10 gallons for a can of lima beans. Textile production requires enormous quantities of water. To produce 1000 lbs. of dyed cotton cloth as much as 50,000 gallons are required. Even the petroleum industry requires 770 gallons of water to refine each barrel of crude oil. These figures are more significant when one realizes that the average domestic consumption is only 50 gallons per capita per day, although this is on the increase as more and more of the population acquire modern plumbing and become more lavish in their use of water.

The increased need for water is complicated by the fact that after it is used the effluent in the form of sewage or industrial waste

is dumped into streams and rivers, often in such quantities that they are rendered unsuitable as sources of potable water. The efforts of various water treatment plants to cope with this problem are highly commendable but sooner or later the raw water that must be processed becomes so badly contaminated that a perfect or even satisfactory job is impossible. Strangely enough, the public criticism that develops is usually directed against the local water bureau which is accused unjustly of inefficiency.

As surface water sources become unfit for use, ground water from deep wells is used more and more. So serious is the drain on this source that water tables have been lowered in some areas to the point that sea water has seeped in, thus destroying this last source of supply. On the west coast of the United States grave concern has developed lest a water shortage will curb further industrial growth and limit the present development of irrigation farming.

It would appear that one solution to the problem, at least in many regions, is to curb the extensive pollution of streams and rivers which might serve as a source of raw water. Not only is this desirable as a means of improving the supply of water but it is also high time that our streams and rivers cease being made open sewers for sewage and industrial waste. A town or an industrial plant upstream has no moral or legal right to contaminate a river so that it is unfit for use by those who are located geographically downstream. The magnitude of pollution in some areas is unbelievable. During the war the masters of vessels putting into the port of Philadelphia protested that the Delaware river was so contaminated that it corroded the hulls of their ships and that the stench was so great in the summer that the crew could not sleep aboard. This was not an exaggeration as we can attest.

It is tragic when one sees the filth and muck that now courses down the Delaware to realize that once this great river was a crystal clear stream, abounding in fish and enjoyed by many for its recreational facilities. In this particular area steps are now being taken to restore this great river to a reasonable degree of cleanliness. The efforts of a group of public spirited citizens, including Governor Duff of Pennsylvania, are largely responsible for the progress being made but some municipalities and industries have been so uncooperative that court action was required to bring about necessary reforms.

Many areas throughout the United States have unabated pollution with no program in effect or planned for its control. One of the most significant steps ever taken to remedy the situation was the passage by Congress of the Water Pollution Control Act of 1948. This authorizes the Public Health Service and the Federal Works Agency, together with the States, to develop a nation-wide program for the abatement of stream pollution. Considerable progress has already been made by the Public Health Service in the preparation of comprehensive pollution abatement programs which are suitable for use by the States in carrying out technically and economically sound action programs. A Water Pollution Control Advisory Board was appointed and its first report has been released. This Board is to bring government and industry together and to work with the various States in the adoption of programs for the abatement of pollution.

This activity by the Federal Government is entirely proper, for pollution is definitely an interstate problem. Water polluted by a city or an industry in one state may, and often does, create a serious problem for those who reside in another. The public should give whole-hearted support to this program and all those interested in public health should enlist public support for this long needed reform.

Pure water like pure air and sunshine is one of man's blessings which no one has a right to take away. Just as we must not permit our liberty to be lost by the growth of government, we must not lose our natural blessings by the growth of cities and industries. Here, at least, is one instance wherein the government may help us keep or even restore a blessing which has all but been taken from us.

L. F. Tice

THE POTENTIATING EFFECTS OF VARIOUS COMPOUNDS ON THE ANTIBACTERIAL ACTIVITIES OF SURFACE ACTIVE AGENTS

By Louis Gershenfeld, D. Sc., and Russell L. Stedman, D. Sc.*

Part II

IN Part I of this investigation, the effects of cobalt chloride, 9-amino acridine and Triton N-100, a non-ionic surface active agent, on the bacteriostatic properties of cationic and anionic detergents were presented. The data indicated that effects ranging from a significant inhibition of bacteriostatic activity to a marked increase in bacteriostatic efficiency may result from the addition of these chemicals to the detergents. It was decided to investigate the effect of cobalt chloride, 9-amino acridine and the non-ionic surface active agent, Triton N-100, on the bactericidal activity of a representative cationic compound, Ceepryn, against two test organisms, *E. coli* and *S. aureus*.

The testing of the cationic surface active agents for bactericidal efficiency remains a difficult problem even after much investigation. Discussions of the problem have recently been reviewed elsewhere (1, 2, 3, 4). Among the methods proposed for evaluation of the bactericidal activities of cationic surface active agents is the semi-micro technic of Klarmann and Wright (5).

Purpose

To study the effects of cobalt chloride ($CoCl_2.6H_2O$), 9-amino acridine and a non-ionic surface active agent, Triton N-100, on the bactericidal activity of the cationic detergent, Ceepryn, using a modification of the semi-micro technic of Klarmann and Wright.

Procedure

The original semi-micro technic of Klarmann and Wright consists of using one-tenth the volume of the medicament-organism

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mixture employed in the F. D. A. phenol coefficient method (6). Thus, 0.05 ml. of a twenty-four hour culture of the test organism is added to 0.5 ml. of antiseptic dilution in the seeding tube. Instead of subculturing an aliquot (one loopful) of this mixture as is done in the F. D. A. technic, the semi-micro method consists of adding 20 ml. of broth directly to the tube containing the medicament-organism mixture and incubating the tube and contents.

This technic was devised for the testing of quaternary ammonium compounds. In such tests, the dilution of the medicament-organism mixture (resulting when 20 ml. of broth were added) was sufficient to prevent subsequent bacteriostatic action of the diluted cationic agent on surviving bacteria in the tube. However, in the tests conducted herein, mixtures containing Ceepryn and a second chemical were tested. Further dilution or inactivation was necessary to prevent bacteriostatic action of both chemicals in the mixture on surviving bacteria. Since anionic surface active agents inactivate cationic compounds, an anionic agent was used to inactivate the Ceepryn. The addition of larger quantities of broth to the seeding tubes was also used to dilute the second chemical, if further dilution was found necessary. The following procedure was employed to test the inactivation of Ceepryn by Duponol C, an anionic surface active agent:

Dilutions of 1:20,000, 1:40,000 and 1:80,000 Ceepryn were made. (Such approximate dilutions result when 20 ml. of broth are added to seeding tubes containing 1:500, 1:1000 and 1:2000 Ceepryn in the 0.55 ml. of medicament-organism mixture employed in a semi-micro test (5)). One ml. of each of these dilutions was placed in a series of sterile tubes. Nine ml. of nutrient broth containing various dilutions of Duponol C (from 1:5000 to 1:80,000) were added to each series. Control tubes containing Ceepryn and nutrient broth without Duponol C were also included. All tubes were inoculated with 0.1 ml. of a twenty-four culture of *E. coli,* incubated at 37° C. and observed after five days. The results obtained are recorded in Table I. It will be noted that 1:10,000 Duponol broth is sufficient for inactivation of all dilutions of Ceepryn. Therefore, Duponol C, 1:10,000, was employed as an inactivator in all tests against *E. coli.* In addition, it was found that 20 ml. of

1:10,000 Duponol broth were sufficient to dilute and inactivate both chemicals in tests on mixtures of cobalt chloride and Triton X-100 with Ceepryn. With combinations of 9-amino acridine and Ceepryn, however, 40 ml. of 1:10,000 Duponol broth were necessary to inactivate both antiseptics. The use of twice the usual amount of 1:10,000 Duponol broth did not effect the results obtained with Ceepryn alone.

The above procedure was repeated using *S. aureus* to determine whether Ceepryn is inactivated by Duponol C in the presence of this organism. The concentrations of Ceepryn employed were 1:100,000, 1:200,000 and 1:400,000. These dilutions approximate

TABLE I

THE INACTIVATION OF CEEPRYN BY DUPONOL C AGAINST E. COLI

Concentration Ceepryn	Concentration Duponol	Ratio Anionic: Cationc	Growth After Five Days Incubation at 37° C.
1:20,000	1:5000	4:1	+
1:20,000	1:10,000	2:1	+
1:20,000	1:20,000	1:1	+
1:40,000	1:5000	8:1	+
1:40,000	1:10,000	4:1	+
1:40,000	1:20,000	2:1	+
1:40,000	1:40,000	1:1	+
1:80,000	1:10,000	8:1	+
1:80,000	1:20,000	4:1	+
1:80,000	1:40,000	2:1	+
1:80,000	1:80,000	1:1	+
1:20,000 control			—
1:30,000 "			—
1:40,000 "			+
1:50,000 "			+
	1:5000 control		+

+ growth
— no growth

those obtained when 20 ml. of broth are added to 0.55 ml. of 1:2500, 1:5000 and 1:10,000 Ceepryn in a semi-micro test (5). Varying concentrations of Duponol broth were employed: from 1:20,000 to 1:400,000. The findings are recorded in Table II. From this data, it is noted that 1:100,000 Duponol broth is

TABLE II

THE INACTIVATION OF CEEPRYN BY DUPONOL C AGAINST S. AUREUS

Concentration Ceepryn	Concentration Duponol	Ratio Anionic : Cationic	Growth After Five Days Incubation at 37° C.
1:100,000	1:20,000	5:1	—
1:100,000	1:40,000	2.5:1	—
1:100,000	1:60,000	1.7:1	—
1:100,000	1:80,000	1.3:1	+
1:100,000	1:100,000	1:1	+
1:200,000	1:20,000	10:1	—
1:200,000	1:40,000	5:1	—
1:200,000	1:60,000	3.3:1	—
1:200,000	1:80 000	2.5:1	+
1:200,000	1:100,000	2:1	+
1:200,000	1:200,000	1:1	+
1:400,000	1:40,000	10:1	—
1:400,000	1:60,000	6.7:1	+
1:400,000	1:80,000	5:1	+
1:400,000	1:100,000	4:1	+
1:400,000	1:200,000	2:1	+
1:400,000	1:400,000	1:1	+
1:100,000 control			—
1:200,000 "			—
1:400,000 "			+
1:600,000 "			+
	1:20,000 control		—
	1:40,000 "		+

+ growth
— no growth

adequate for inactivation and this strength of anionic agent was employed in tests against *S. aureus*. Twenty ml. of 1:100,000 Duponol broth were not sufficient, however, to dilute and inactivate both chemicals in mixtures of Ceepryn with cobalt chloride, 9-amino acridine and Triton N-100. Sixty ml. of 1:100,000 Duponol broth were found to be adequate and this amount, with one exception, was employed in all tests against *S. aureus*. With certain concentrations of Ceepryn and Triton N-100 mixtures, however, a special dilution procedure was necessary to prevent bacteriostatic action on survivors: twenty ml. of 1:100,000 Duponol broth were added to the medicament-organism mixture after the 5, 10 or 15 minute exposure time had elapsed. The entire 20 ml. were then subcultured into 300 ml. of 1:100,000 Duponol broth. An additional amount of 20 ml. of 1:100,000 Duponol broth was then added to the original tube after the subculturing. Both the original tube and the subculture were then incubated.

To summarize, the following modification of the original Klarmann and Wright semi-micro technic was employed in this study: dilutions of Ceepryn, a second potentiating agent (cobalt chloride, 9-amino acridine or Triton N-100) and mixtures of the two were made. One-half ml. of each dilution was placed in each of three sterile, wide-mouthed bottles of 65 ml. capacity (the three bottles representing the 5, 10 and 15 minute exposure periods). All bottles were inoculated with 0.06 ml. of a twenty-four hour culture of either *E. coli* or *S. aureus;* calibration of the pipettes employed indicated that one drop of a twenty-four hour culture of these organisms was equivalent to 0.06 ml. After the designated exposures at room temperature (25° C.), Duponol broth was added, the quantity of broth and concentration of Duponol depending on the mixture and test organism concerned as previously mentioned. All bottles were incubated at 37° C. for a five day period and observations made at the end of this time. All bottles showing no growth were then checked for bacteriostasis by the following procedure: negative bottles were again inoculated with 0.06 ml. of a twenty-four hour culture of the test organism employed in the bactericidal test. These bottles were incubated at 37° Centigrade. After five days incubation, readings were again made. Bottles in which no growth occurred indicated bacteriostasis. Throughout the study, however, the

results obtained by such a procedure indicated that the inactivation steps outlined above were adequate to prevent bacteriostasis.

Major differences between the original semi-micro technic and the modifications used in this study are summarized herein:

	Original Technic		Modified Technic	
	E. coli	*S. aureus*	*E. coli*	*S. aureus*
Seeding tubes	Test tubes, 25 by 150 mm.		Square, wide-mouthed, screw-neck bottles of 65 ml. capacity, 35 mm. x 85 mm. (diam. opening, 20 mm.)	
Inoculum	0.05 ml. of a twenty-four hour culture		0.06 ml. of a twenty-four hour culture	
Medium	Nutrient broth	Nutrient broth with serum or Bacto oxgall	1:10,000 Duponol broth	1:100,000 Duponol broth
Quantity of medium added to medicament-organism mixture	20 ml.		20 ml.*	60 ml.**

* Forty ml. employed in tests on Ceepryn-9-amino acridine mixtures.

** A special procedure was necessary with certain concentrations of Ceepryn-Triton N-100 mixtures. For details, see "Procedure".

The nutrient broth, surface active agents, chemicals and test organisms were the same as those employed in Part I of this study.

Findings

A. The effect of cobalt chloride on the bactericidal efficiency of the cationic surface active agent, Ceepryn

I. In tests employing *E. coli.*

The addition of cobalt chloride, 1:200, to solutions of Ceepryn increased the bactericidal efficiency of this compound (Table III). The following dilutions were bactericidal in 10 minutes:

a. Ceepryn solution, 1:3000.

b. Ceepryn solution, 1:10,000, with cobalt chloride, 1:200.

Cobalt chloride solution, 1:200, did not kill in 15 minutes.

TABLE III

THE BACTERICIDAL ACTIVITY OF COBALT CHLORIDE-CEEPRYN MIXTURES AGAINST E. COLI—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Minutes 5	Minutes 10	Minutes 15
1:1000	Ceepryn	—	—	—
1:3000	"	+	—	—
1:5000	"	+	+	+
1:7000	"	+	+	+
1:1000	Ceepryn with 1:200 cobalt chloride	—	—	—
1:3000	"	+	—	—
1:5000	"	+	—	—
1:7000	"	+	—	—
1:10,000	"	+	—	—
1:1000	Ceepryn with 1:500 cobalt chloride	—	—	—
1:3000	"	+	—	—
1:5000	"	+	+	+
1:7000	"	+	+	+
1:10,000	"	+	+	+
1:200	Cobalt chloride	+	+	+

\+ growth
— no growth

2. In tests employing *S. aureus.*

The admixture of cobalt chloride, 1:200, increased the bactericidal efficiency of Ceepryn (Table IV). The following dilutions were bactericidal in 5 minutes:

a. Ceepryn solution, 1:3000.

b. Ceepryn solution, 1:5000, with cobalt chloride, 1:200.

Cobalt chloride solution, 1:200, did not kill in 15 minutes.

TABLE IV

THE BACTERICIDAL ACTIVITY OF COBALT CHLORIDE-CEEPRYN MIXTURES AGAINST S. AUREUS—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration	Minutes 5	Minutes 10	Minutes 15
1:3000 Ceepryn	—	—	—
1:5000 "	+	+	+
1:7000 "	+	+	—
1:10 000 "	+	+	+
1:3000 Ceepryn with 1:200 cobalt chloride	—	—	—
1:5000 "	—	—	—
1:7000 "	+	+	—
1:10,000 "	+	+	+
1:3000 Ceepryn with 1:500 cobalt chloride	—	—	—
1:5000 "	+	—	+
1:7000 "	+	+	+
1:10,000 "	+	+	+
1:200 Cobalt chloride	+	+	+

\+ growth

— no growth

B. The effect of 9-amino acridine on the bactericidal efficiency of the cationic surface active agent, Ceepryn

1. In tests employing *E. coli.*

The bactericidal activity of mixtures of 9-amino acridine and Ceepryn was greater than that of the individual agents in the mixture (Table V). The following dilutions killed the test organism in 10 minutes:

a. Ceepryn solution, 1:3000.

b. Ceepryn solution, 1:15,000, with 9-amino acridine, 1:600.

c. Ceepryn solution, 1:10,000, with 9-amino acridine, 1:1000.

No bactericidal effect was noted with 9-amino acridine solutions, 1:600 and 1:1000, after 15 minutes exposure. (The maximum solubility of 9-amino acridine in distilled water is 1:300).

TABLE V

THE BACTERICIDAL ACTIVITY OF CEEPRYN—9-AMINO ACRIDINE MIXTURES AGAINST E. COLI—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration	Minutes 5	Minutes 10	Minutes 15
1:1000 Ceepryn	+	—	—
1:3000 "	+	—	—
1:5000 "	+	+	+
1:7000 "	+	+	+
1:3000 Ceepryn with 1:600 9-mino acridine	—	—	—
1:5000 "	—	—	—
1:7000 "	—	—	—
1:10,000 "	—	—	—
1:15,000 "	+	—	—
1:3000 Ceepryn with 1:1000 9-amino acridine	—	—	—
1:5000 "	+	—	—
1:7000 "	+	—	—
1:10,000 "	+	—	—
1:600 9-amino acridine	+	+	+
1:1000 "	+	+	+

\+ growth
— no growth

2. In tests employing *S. aureus.*

An increase in bactericidal efficiency was noted with mixtures of 9-amino acridine and Ceepryn (see Table VI). The following dilutions were bactericidal in 5 minutes:

a. Ceepryn solution, 1:5000.

b. Ceepryn solution, 1:10,000, with 9-amino acridine, 1:600.

c. Ceepryn solution, 1:7000, with 9-amino acridine, 1:1000.

9-amino acridine solution, 1:600 and 1:1000, did not kill within the 15 minute exposure.

TABLE VI

THE BACTERICIDAL ACTIVITY OF CEEPRYN—9-AMINO ACRIDINE MIXTURES AGAINST S. AUREUS—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Minutes 5	Minutes 10	Minutes 15
1:3000	Ceepryn	—	—	—
1:5000	"	—	—	—
1:7000	"	+	+	—
1:10,000	"	+	+	—
1:3000	Ceepryn with 1:600 9-amino acridine	—	—	—
1:5000	"	—	—	—
1:7000	"	—	—	—
1:10,000	"	—	—	—
1:15,000	"	+	—	+
1:20,000	"	+	+	+
1:3000	Ceepryn with 1:1000 9-amino acridine	—	—	—
1:5000	"	—	—	—
1:7000	"	—	—	—
1:10,000	"	+	—	—
1:15,000	"	+	+	+
1:600	9-amino acridine	+	+	+
1:1000	"	+	+	+

\+ growth
— no growth

C. The Effect of Triton N-100, a non-ionic surface active agent, on the bactericidal efficiency of Ceepryn

1. In tests employing *E. coli.*

The addition of Triton N-100 to solutions of Ceepryn resulted in the inactivation of the bactericidal activity of the cationic agent (Table VII). From two to four times as much Triton as Ceepryn were required for this inactivation. A 1:2000 solution of Ceepryn killed in 5 minutes. When combined with Triton N-100, 1:50, however, a concentration of 1:200 Ceepryn was not bactericidal in 15 minutes. No bactericidal activity was noted with Triton N-100 solution, 1:50, after 15 minutes exposure.

2. In tests employing *S. aureus.*

No increase in bactericidal efficiency was noted with Triton N-100 when combined with Ceepryn (see Table VIII). Inactivation of the bactericidal activity of the cationic agent occurred in mixtures containing high concentrations of Triton N-100. Ceepryn solution, 1:10,000, killed in 10 minutes. When combined with a 1:50 dilution of Triton, Ceepryn solution, 1:1000, was bactericidal in 10 minutes. No bactericidal activity was noted with Triton N-100 solution, 1:50, after 15 minutes exposure.

Summary

The *in vitro* bactericidal activities of mixtures of Ceepryn with cobalt chloride ($CoCl_2.6H_2O$), 9-amino acridine and the non-ionic surface active agent, Triton N-100, were investigated using a modification of the Klarmann and Wright semi-micro technic.

Conclusions

The *in vitro* bactericidal efficiency of solutions of Ceepryn against *E. coli* and *S. aureus* was increased by the addition of cobalt chloride solution, 1:200, or 9-amino acridine solutions, 1:600 and 1:1000.

The *in vitro* bactericidal action of solutions of Ceepryn against *E. coli* and *S. aureus* was inactivated by suitable concentrations of the non-ionic surface active agent, Triton N-100. Triton N-100 in strengths greater than 1:500 were required to obtain this effect.

TABLE VII

THE BACTERICIDAL ACTIVITY OF MIXTURES OF CEEPRYN AND A NON-IONIC SURFACE ACTIVE AGENT (TRITON N-100) AGAINST E. COLI—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Minutes 5	Minutes 10	Minutes 15
	CEEPRYN WITH 1:50 TRITON N-100			
1:1000	Ceepryn	—	—	—
1:2000	"	—	—	—
1:3000	"	+	—	—
1:5000	"	+	+	+
1:200	Ceepryn with 1:50 Triton	+	+	+
1:500	"	+	+	+
1:1000	"	+	+	+
1:50	Triton	+	+	+
	CEEPRYN WITH 1:100 TRITON N-100			
1:2000	Ceepryn	—	—	—
1:3000	"	—	—	—
1:5000	"	+	—	—
1:7000	"	+	+	—
1:200	Ceepryn with 1:100 Triton	+	+	+
1:500	"	+	+	+
1:1000	"	+	+	+
1:100	Triton	+	+	+
	CEEPRYN WITH 1:500 TRITON N-100			
1:1000	Ceepryn	—	—	—
1:2000	"	+	—	—
1:3000	"	+	—	—
1:5000	"	+	+	+
1:500	Ceepryn with 1:500 Triton	—	—	—
1:1000	"	+	—	—
1:2000	"	+	+	+
1:500	Triton	+	+	+
	CEEPRYN WITH 1:1000 TRITON N-100			
1:1000	Ceepryn	—	—	—
1:2000	"	+	—	—
1:3000	"	+	+	+
1:500	Ceepryn with 1:1000 Triton	—	—	—
1:1000	"	—	—	—
1:2000	"	+	+	+
1:3000	"	+	+	+
1:1000	Triton	+	+	+

+ growth
— no growth

TABLE VIII

THE BACTERICIDAL ACTIVITY OF MIXTURES OF CEEPRYN AND A NON-IONIC SURFACE ACTIVE AGENT (TRITON N-100) AGAINST S. AUREUS—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Minutes 5	Minutes 10	Minutes 15
	CEEPRYN WITH 1:50 TRITON N-100			
1:5000	Ceepryn	—	—	—
1:7000	"	+	—	—
1:10,000	"	+	—	—
1:1000	Ceepryn with 1:50 Triton *	+	—	—
1:3000	" *	+	+	+
1:5000	" *	+	+	+
1:7000	" *	+	+	+
1:50	Triton	+	+	+
	CEEPRYN WITH 1:100 TRITON N-100			
1:3000	Ceepryn	+	—	—
1:5000	"	+	—	—
1:7000	"	+	+	—
1:10,000	"	+	+	+
1:3000	Ceepryn with 1:100 Triton *	+	+	+
1:5000	" *	+	+	+
1:7000	" *	+	+	+
1:10,000	"	+	+	+
1:100	Triton	+	+	+
	CEEPRYN WITH 1:500 TRITON N-100			
1:3000	Ceepryn	—	—	—
1:5000	"	—	—	—
1:7000	"	+	+	+
1:10,000	"	+	+	+
1:3000	Ceepryn with 1:500 Triton	—	—	—
1:5000	"	+	+	+
1:7000	"	+	+	+
1:500	Triton	+	+	+
	CEEPRYN WITH 1:1000 TRITON N-100			
1:3000	Ceepryn	—	—	—
1:5000	"	+	+	+
1:7000	"	+	+	+
1:3000	Ceepryn with 1:1000 Triton	—	—	—
1:5000	"	+	+	+
1:7000	"	+	+	+
1:1000	Triton	+	+	+

\+ growth
— no growth

* These bottles required further dilution beyond the 60 ml. of 1:100,000 Duponol broth usually added (see "Procedure").

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RADIOACTIVE MATERIALS AND THEIR MEDICAL USES*

By S. B. Osborn, B. Sc., A. Inst. P.**

THE rapid increase in the use of radioactive materials in recent years would seem to justify a note on some of their properties, dangers and medical uses, though, as has already been mentioned in THE JOURNAL (1), most pharmacists are unlikely to have any direct contact with such materials. Their uses in medical diagnosis should, however, be noted especially by those responsible for teaching.

Nature of Radioisotopes

Every element can exist in the several forms (2) which differ in the number of neutrons in the atomic nucleus. A change in the number of these neutrons will not alter the nuclear charge (the atomic number, which determines chemical properties), but may make the atomic nucleus unstable. Its instability results in the partial breakup of the nucleus, with the emission of particles, or gamma rays, or both, and the emergence of a stable nucleus, possibly of a different element. The presence of such unstable nuclei can be detected, and the quantity of radioactive material estimated, by the radiations emitted.

The radioactivity of a particular specimen of a radioisotope will be reduced exponentially as the material undergoes a particular transformation. That is, the time in which the activity decays to one-half is the same as the time required for the decay from $\frac{1}{2}$ to $\frac{1}{4}$, from $\frac{1}{4}$ to $\frac{1}{8}$, and so on, and is known as the half-life, which may have any value between 10^{-15} seconds and 100,000 years. For medical purposes, it is usually convenient to choose an isotope with a half-life measured in hours, days, or weeks. If it is very short, transport from the production site to the place of use, and chemical (or other) manipulations, will occupy too large a portion of the useful life of the material; if it is too long, on the other hand, the activity of any given mass is small, and measurement may become more

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difficult. In addition, the radiation dose delivered to a patient usually increases as the half-life increases, and (unless one is using the material therapeutically), this should be reduced to the minimum.

Since any element can be prepared in a radioactive form, it is possible to "label" a particular specimen of material by incorporating in it a known proportion of a radioisotope; the labelled specimen can be traced (by its radiations), and its chemical form evaluated, in the presence of any diluent, including material which is identical but unlabelled.

Measurements

A Geiger-Müller counter is almost invariably used for the measurement of radioactivity. This is a device which allows a small current to pass momentarily when a penetrating ray or ionising particle passes through its sensitive volume. Each ray or particle activates the counter, thus permitting minute traces of radioactive material to be easily detected and assayed. The pulses of current are amplified, and used to operate counting equipment. Frequently this consists of valve networks which divide the number of pulses by 2, 8, 10, or some other convenient number, before operating a mechanical counting relay. Such a unit (known as a scaler (3)) commonly counts up to a million pulses before repeating.

Measurements are complicated by the presence of "background" radiation, which consists of cosmic rays, radiation arising from the natural radioactivity of the earth, etc. This radiation cannot be eliminated, but it can be minimised by heavy lead screening, and this is done whenever possible. The remaining background is measured by counting the number of pulses from the G. M. counter in a given time and thus obtaining for the background an average of b counts per minute. A specimen of radioactive material is then placed in a known position near the counter, and if the counting rate is now a counts per minute, the counting rate due to the specimen alone is $(a\text{-}b)$ counts per minute.

The fact that all radioactive work is subject to random statistical fluctuations introduces an uncertainty into any estimate of counting rate. It is found (4), however, that if N pulses have been counted in T minutes, then the measured counting rate is N/T counts per minute, and the standard deviation $\sqrt{N}/T$. The probable error (the

error which is as likely to be exceeded as not) is then $0.67\sqrt{N/T}$, and it is easy to see that, relative to N/T, this error is large when N is small. Thus, if a measurement is required with a standard deviation of 1 per cent., it is necessary to time the counting of 10,000 pulses ($\sqrt{10{,}000}=100=1$ per cent of 10,000), whereas if an inaccuracy of 10 per cent. is admissible, only 100 pulses need be timed. This holds good whatever the counting-rate, provided that this is not high enough for the characteristics of scaler and counter to interfere. These usually have resolving times well below 0.001 seconds.

Assay

Assaying involves estimating the activity (and hence the quantity of radioactive material) in a given sample, and different methods are used in different circumstances.

(*a*) Solutions which can be evaporated to dryness (for assay, solids can be converted into such solutions). A small, known volume of solution is evaporated to dryness on a small metal disc, sometimes of special shape (4a), which is placed in a standard position relative to a counter, usually in a lead "castle," and the counting rate determined.

(*b*) Solutions which it is inconvenient to evaporate to dryness. For these a counter is used which holds a known quantity of the liquid in a jacket separated from the active portion of the counter by a thin glass wall (5).

(*c*) Gases. The type of counter described under (*b*) can be used if there are reasonably large quantities of radioactive materials present. More sensitive methods have been devised, which are appropriate to a research laboratory with facilities for high vacuum work (6). Alternatively, the gas can be mixed with the air in an ionisation chamber (6a). Generally speaking, the assay of small quantities of radioactive gases is not easy.

Assaying is complicated by two phenomena which must be taken into account.

(i) If the radiation being measured is β-radiation (emission of electrons) or soft, easily absorbed, γ-radiation, an appreciable

fraction may be absorbed in the sample itself, or in the window of the counter. Mica windows less than 0.01 mm. thick can be used, and the radioactive material spread in a very thin film, but occasionally large corrections are still necessary.

(ii) If the radiation is penetrating γ-radiation, only a small proportion of rays will be absorbed in the counter, and thus be recorded. This proportion will depend on the wavelength of the γ-rays, and also on the materials of which the counter is made, and is difficult to assess with accuracy.

Before any assay can be made, therefore, it is necessary to know what number of counts per minute corresponds to, say, one micro-curie,[1] in the particular experimental arrangement used. This is not usually done by any absolute method (which is laborious), but by using material previously assayed by a counter already calibrated. In addition, it is sometimes possible to assay the radioactive content of an organ *in vivo* provided it is fairly small and its position accurately known. A given counter can then be calibrated in counts per minute per micro-curie at a standard distance and then the organ assayed at this distance. Allowance must be made (i) for radiation which is absorbed by any overlying tissues, (ii) for that which, although it leaves the organ in some other direction, is scattered by the tissues through which it passes so that it is deflected back towards the counter, and (iii) for any which arises from the rest of the body and penetrates the shielding of the counter.

Preparation

Preparation usually consists of bombarding a suitable material with particles or penetrating radiation. Nuclear changes can be induced, resulting in particular radioactive nuclei being produced, and these may or may not be of the same element as the parent substance. There are some 16 different types of nuclear reaction[2] which can be utilized (7), and the following (for phosphorus) are typical. Not all, however, are equally suitable for large-scale production.

[1] One micro-curie corresponds to 37,000 nuclear disintegrations per second.

[2] Note that the total atomic charge (subscript) and total atomic weight (superscript) are the same before and after the reaction takes place.

(*a*) Phosphorus atoms, $_{15}P^{31}$, irradiated by neutrons (in a uranium pile, for instance) may become radiophosphorus, $_{15}P^{32}$, by simple neutron capture. The reaction may be written:

$$_{15}P^{31} + {}_{0}n^{1} \rightarrow \gamma\text{-ray} + {}_{15}P^{32}$$

$_{15}P^{32}$ is spontaneously radioactive (half-life 14.3 days) as follows:—

$$_{15}P^{32} \rightarrow {}_{16}S^{32} + {}_{-1}e^{0} \text{ (a } \beta\text{-ray)}$$

(*b*) *Chlorine*, $_{17}Cl^{35}$, may capture a neutron and emit an α-ray:

$$_{17}Cl^{35}, + {}_{0}n^{1} \rightarrow {}_{2}He^{4} + {}_{15}P^{32}$$

(*c*) Sulphur, $_{16}S^{32}$, may capture a neutron and emit a proton:

$$_{16}S^{32} + {}_{0}n^{1} \rightarrow {}_{1}H^{1} + {}_{15}P^{32}$$

(*d*) Aluminum, $_{13}Al^{27}$, if irradiated by α-rays, may capture one and emit a neutron:

$$_{13}Al^{27} + {}_{2}He^{4} \rightarrow {}_{0}n^{1} + {}_{15}P^{30}$$

$_{15}P^{30}$ is another radioisotope of phosphorus (half-life 2.2 minutes) which decays as follows:

$$_{15}P^{30} \rightarrow {}_{14}Si^{30} + {}_{1}e^{0} \text{ (a positron)}$$

(*e*) Phosphorus, $_{15}P^{31}$, irradiated with protons, may emit a neutron:

$$_{15}P^{31} + {}_{1}H^{1} \rightarrow {}_{0}n^{1} + {}_{16}S^{31}$$

The atomic weight of the nucleus is unaltered, but it has become radiosulphur (half-life 3.2 seconds) which decays as follows:

$$_{16}S^{31} \rightarrow {}_{15}P^{31} + {}_{1}e^{0}$$

(*f*) Phosphorus, $_{15}P^{31}$, irradiated with γ-rays, may emit a neutron:

$$_{15}P^{31} + \gamma\text{-ray} \rightarrow {}_{0}n^{1} + {}_{15}P^{30}$$

Nuclear reactions such as these may be induced in a uranium pile, in a cyclotron, or by the rays from radium. Reaction (*c*) is the usual method of producing $_{15}P^{32}$, as it gives a high yield.

When the end-product of such a nuclear reaction is of the same element as the parent, it is difficult to produce a sample containing a high proportion of radioactive material. When a different element is produced, however, chemical separation of the end-product is possible, and very high specific activities can be obtained. It may be noted in passing that when such "carrier-free" preparations are made, the quantity of radio-active material involved is extremely small (perhaps of the order of micro-microgrammes). The radioactive material may be adsorbed on the walls of a containing vessel making dilution and the subdivision of a sample extremely difficult (8). It is usual to add traces (perhaps microgrammes) of inactive material to act as a carrier, and enable the radioactive material to be manipulated more easily.

Certain radioisotopes (of elements whose atomic numbers lie between 35 and 55) can be extracted as fission products from the uranium pile. In the production of plutonium or other fissile material (the chief function of a pile), appreciable quantities of uranium and other elements undergo fission, producing a wide variety of radioisotopes which can be extracted chemically. This, of course, is done in a special remote-controlled laboratory, in view of the dangerous quantities of radiation emitted. Iodine and strontium, in particular, can be prepared by this method.

Similarly, any chemical processing of a radioisotope before use must be done in such a way as to reduce to the minimum the radiation dosage received by the workers concerned. This may necessitate the use of special apparatus such as lead-fronted benches, long-handled forceps, and dust-extractor fans, and also instruments for estimating quickly the amount of radiation to which the staff may be exposed. The disposal of radioactive waste must also be undertaken with care, partly because of the possibility of adsorption in laboratory waste pipes, and consequent interference with the work in progress, and partly for the sake of the safety of the sewerage workers. Such problems are discussed in a recent publication by the Medical Research Council and the Atomic Energy Research Establishment (9).

Should sterilisation be necessary before radioactive material can be used clinically, this can easily be done, as changes in temperature do not in any way affect radioactive properties.

Medical Uses of Radiosotopes

Tracers

The field of research opened up by radioisotopes is almost limitless, and much work is being done at the moment in studying physiological processes by this means. Any radioisotope introduced into the body retains its chemical identity and, at the same time, emits radiations which enable it to be traced, and its quantity to be assayed, allowance being made when necessary for the decay in the material during a test. Any particular labelled sample can be detected and assayed even if diluted with other, unlabelled, samples of the same material. It is impossible here to give even a summary of the work that is being done along these lines, and references should be made to the works on the subject (10).

Two main lines of investigation may be noted:

(i) A great deal of work has been done on the metabolism and excretion of proteins (labelled with nitrogen or sulphur), of carbohydrates and lipides (mostly labelled with carbon) and of mineral elements such as phosphorus, calcium, strontium, iodine, iron, copper, cobalt, manganese and zinc. Iron has also been used to label red blood corpuscles in order to estimate their life. Sulphur is being used to investigate the uptake and excretion of penicillin (11).

(ii) The distribution of an element in an organ can be shown by means of an autoradiograph. This has been particularly useful in the case of radioiodine in the thyroid. At a suitable time before the gland is to be removed, radioiodine is administered, and after removal it is fixed and sectioned in the ordinary way. The section can then be pressed against a suitable X-ray emulsion, which will be blackened in the vicinity of radioiodine. A recent technique (12) enables film and section to be superimposed, and the iodine-concentrating areas of particular cells inspected microscopically. Such methods facilitate research into certain histological and cytological problems.

Aids to Diagnosis

From the mass of work done with tracers it is already possible to evaluate some uses of radioisotopes which are of help in diagnosis.

This aspect of radioisotope work will expand as tracers increase our knowledge of the body's processes. The elements so far used in diagnostic work are:

(i) Iodine for the measurement of thyroid activity, and for localisation of functional metastases from carcinomas of the thyroid.

(ii) Phosphorus for the estimation of blood volume, and for differentiation of carcinoma of the breast from inflammatory conditions.

(iii) Sodium for the estimation of extracellular fluid and of rate of blood circulation, and also for the determination of the level at which a limb should be amputated in gangrene due to arterial disease or damage.

(i) *Iodine.*—Almost all the iodine of the body is normally concentrated in the thyroid gland, and, since the iodine content of the plasma is small, it is found that results obtained by the administration of radioiodine depend on the amount of inactive iodine administered at the same time. Table 1 (13) shows this clearly, and also the

TABLE I

Amount of iodine admininistered	Type of subject	Percentage of dose administered [3] which is localised in the thyroid at the end of:			
		1 hour	1 day	2 days	5 days
14 mgm.	Normal	1.5	3.5	3.8	3.8
	Toxic goitre	13.5	5.0	5.0	5.0
	Non-toxic goitre	5.0	9.0	10.0	10.0
	Hypothyroidism without goitre	0.5	0.5	0.5	0.5
0.1 μgm.	Normal	4.0	18.0	19.0	19.0
	Toxic goitre	48.0	61.0	58.0	49.0
	Non-toxic-goitre	10.0	25.0	25.0	25.0
	Hypothyroidism without goitre	0.5	2.0	3.0	3.0

[3] Allowance is made, of course, for decay since administration.

variations of iodine uptake which depend upon the activity of the gland. The figures quoted are, of course, averages only, and there are considerable individual differences.

Carcinoma of the thyroid is not common, and in most cases the growth has not the ability to concentrate iodine. Occasionally, however, a growth is found which is derived from iodine-concentrating tissue and the metastases will then be iodine-concentrating also. If, in such a case, radioiodine be administered and the body searched with a G.-M. counter, metastases can be located by their content of radioiodine more easily than by ordinary clinical methods (14).

It has also been reported that intrathoracic goitre can be diagnosed and localised with radioiodine by plotting the area over which a directional counter gives a high response (15).

(ii) *Phosphorus.*—If a small quantity of blood is taken from a subject and shaken with radiophosphorus for some time, an appreciable amount of the radioisotope will be taken up by the corpuscles. This labelled blood can be reinjected into the subject and blood samples withdrawn at intervals (16). The activity of these samples will exhibit considerable fluctuations for the first minute or two, and then, as mixing becomes complete, the activity can be used to assess the degree of dilution of the labelled blood by unlabelled blood, and hence the total blood volume. In certain cases of cardiac dilatation, the fluctuations take several minutes to die away.

It is also reported (17) that radiophosphorus is absorbed more strongly in a breast carcinoma than in non-malignant tissue, and that this can be used as a test for differentiating between an inflammatory condition and a carcinoma. A β-ray counter over such a concentrating area gives a counting rate over 25 per cent. higher than when placed over normal tissue; if a tumour is benign, the increase is much smaller than this. Such a test, however, is only applicable to superficial tumours, as 1/4 in. of overlying tissue would absorb all the β-rays emitted.

(iii) *Sodium.*—The volume of extra-cellular fluid of the body can be determined with sodium (18). Normal saline, containing a small proportion of $Na^{24}Cl$ is introduced into the blood plasma, and the concentration of the Na^{24} determined some hours later. Assum-

ing that complete and uniform mixing has taken place, the volume of fluid into which the Na^{24} has diffused can be calculated.

Blood circulation times have been estimated with radiosodium (19). Normal saline containing Na^{24} is injected into the antecubital vein and detected by a counter under the foot, the time interval being measured. This has been found to vary between 15 and 60 seconds, the average being 45 seconds. Arm-to-arm times have also been measured, and in children these are frequently between 5 and 15 seconds (20). It has been noticed (19), however, that the radiosodium content of a limb only reaches an equilibrium level after several hours, and that, in normal subjects, the range of varibility from the average rate of uptake seldom exceeds 15 per cent. Cases of scleroderma and Raynaud's disease, however, showed an uptake curve very much slower than the normal.

If radiosodium is injected into a gangrenous limb, it is possible to locate the optimum site for amputation. When the radiosodium is nearing equilibrium in the extra-cellular fluid of the normal tissues, it will be found that response from the affected area is relatively low because of its poor blood supply. Amputation, which should remove all the tissues with an impaired blood supply, can then be carried out with certain knowledge of the extent of the gangrenous tissue.

Estimation of the rate of flow of venous blood in the leg has also been made using Na^{24} as saline, with a view to investigating the effect of this on the production of venous thrombosis (21). In this case, the saline is injected into a vein in the foot, and detected as it passes the femoral triangle. The time taken for venous blood to travel this distance in normal subjects is between 4 and 50 seconds. Women in labour normally have a much slower rate of flow, and times of 2 to 3 minutes have been recorded (22). Further research may well demonstrate that an unusually slow rate of flow is associated with an increasing probability of femoral thrombosis, and that the test may then be used to estimate the likelihood of thrombosis in a particular patient.

In Therapy

In certain diseases, radioisotopes can be used therapeutically (23), since radiations comparable in effect with X-rays and the rays from radium can be generated within affected organs. An

iodine-concentrating carcinoma of thyroid (24), for instance (and its metastases (25) can be treated by administering large quantities of radioiodine which are selectively absorbed, and a similar treatment has been used for hyperthyroidism (26). Phosphorus, because of its selective absorption in bone and rapidly-growing tissue, has been used therapeutically (27) for polycythemia vera (28), Hodgkin's disease (29), and various leukemias (30) and lymphosarcomas (31). It appears to be of particular use in polycythemia vera. Radiostrontium, which behaves similarly to calcium in the body, has been used in treating generalised carcinomatosis of bone (32).

Conclusion

Radioisotopes offer extremely powerful tools to medicine, and it will take a number of years for their best uses to be evaluated. We can say already, however, that they can be used to assist in the diagnosis and treatment of certain types of disease. They can be most dangerous, unless properly used, and this has necessitated legislation (33) to protect the community from their abuse. All applications for radioisotopes for medical purposes in this country must be made through the Medical Research Council, who have published a booklet on the control of the hazards involved (9).

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NEW ADMISSIONS AND DELETIONS TO THE U. S. P. XIV.

RAPID progress is being made toward the release of the U. S. P. XIV. The selection of drugs for inclusion in the Pharmacopeia is a task which, today, is made difficult by the rapidly expanding list of therapeutic agents.

The subcommittee on scope in making its selection keeps in mind the original premise stated in the first Pharmacopeia that its objective is "to select from among substances which possess medicinal power, those the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage."

Many of the new items admitted to the U. S. P. XIV are well-known to physicians and pharmacists under trade-marked names but such names cannot be used in the Pharmacopeia, only uncontrolled titles. For this reason many new names must be devised for official use. Fortunately some of the new U. S. P. titles were previously adopted by the A. M. A. Council for use in New and Non-official Remedies and are familiar to many. Other titles are entirely new. These were devised by the Nomenclature Subcommittee, and usually consist of a shortened chemical name.

In the following list of "new admissions" trade-marked names have been placed in parenthesis after some of the proposed official titles so that the items may be identified. *The trade-marked titles will not appear in the Pharmacopeia.*

A few titles are listed which may not appear in the printed book due to the impossibility of completing standardization studies. Such items will be made official by Interim Revision Supplements, when acceptable standards become available.

Articles Added to U. S. P. XIV

Acacia Syrup
Acetanilid Tablets
Acetic Acid
Acetylsalicylic Acid Capsules
Albumin, Normal Human Serum
Aluminum Acetate Solution
Aluminum Subacetate Solution
Aluminum Sulfate
Aminophylline Suppositories
Ammonium Mandelate Tablets
Amphetamine
Amphetamine Sulfate
Amphetamine Sulfate Tablets
Aureomycin Hydrochloride
Aureomycin Hydrochloride Capsules

Benzyl Benzoate Chlorophenothane Lotion
Biscumarol (Dicumarol)
Biscumarol Capsules
Biscumarol Tablets
Butopyronoxyl (Indalone)
Cacao
Cacao Syrup
Calciferol (Vitamin D_2)
Calcium Gluconate Tablets
Calcium Lactate Tablets
Calcium Mandelate Tablets
Carbarsone Capsules
Carbarsone Suppositories
Carbarsone Tablets
Castor Oil, Sulfated
Cellulose, Oxidized
Cherry Juice
Cherry Syrup
Chloramphenicol (Chloromycetin)
Chloramphenicol Capsules
Chloramphenicol Tablets
Chloroguanide Hydrochloride (Paludrine)
Chloroguanide Hydrochloride Tablets
Chlorophenothane (D. D. T.)
Chloroquine Phosphate
Chloroquine Phosphate Tablets
Chorionic Gonadotrophin
Chorionic Gonadotrophin Injection
Congo Red
Congo Red Injection
7-Dehydrocholesterol, Activated (Vitamin D_3)
Desoxycorticosterone Acetate Injection
Desoxycorticosterone Acetate Pellets
Dihydromorphinone Hydrochloride Injection
Dihydrostreptomycin
Diiodohydroxyquinoline (Diiodoquin)
Diiodohydroxyquinoline Tablets
Dimercaprol (BAL)
Dimercaprol Injection
Dimethyl Phthalate (Insect Repellent Ingredient)
Dimethyl Phthalate Solution, Compound
Diphenhydramine Hydrochloride (Benadryl)
Diphenhydramine Hydrochloride Capsules
Diphtheria Toxoid and Pertussis Vaccine Combined
Ephedrine Hydrochloride Capsules
Ephedrine Hydrochloride Tablets
Ephedrine Sulfate Capsules
Ephedrine Sulfate Injection
Epinephrine in Oil Injection
Epinephrine Bitartrate
Epinephrine Bitartrate Ophthalmic Ointment
Epinephrine Bitartrate Ophthalmic Solution
Ergotamine Tartrate Injection
Estradiol Tablets
Estradiol Benzoate Injection
Estrogenic Substances
Estrogenic Substances Capsules
Estrogenic Substances Injection
Estrogenic Substances Tablets
Estrone Injection
Ethohexadiol
Ferrous Sulfate Syrup
Folic Acid
Folic Acid Capsules
Folic Acid Tablets
Globulin, Antihemophilic (Blood Fraction I)
Heparin Sodium
Heparin Sodium Injection
Homatropine Methylbromide
Homatropine Methylbromide Tablets
Insulin, Globin Zinc, Injection
Iodoalphionic Acid (Priodax)
Iodoalphionic Acid Tablets
Iodochlorohydroxyquin (Vioform)
Iodochlorohydroxyquin Powder, Compound
Lactic Acid
Liver with Stomach Capsules
Mannitol Hexanitrate Tablets
Menadione Capsules (in oil)
Menadione Injection
Meperidine Hydrochloride (Demerol Hydrochloride)
Meperidine Hydrochloride Injection

Meperidine Hydrochloride Tablets
Meralluride (Mercuhydrin Sodium)
Meralluride Injection
Mercurophylline
Mercurophylline Tablets
Mercury Ammoniated Ophthalmic Ointment
Mercury Bichloride
Mercury Bichloride Ophthalmic Ointment
Mersalyl and Theophylline Tablets
Methamphetamine Hydrochloride (Desoxyephedrine)
Methiodal Sodium (Skiodan)
Methiodal Sodium Injection
Naphazoline Hydrochloride (Privine Hydrochloride)
Naphazoline Hydrochloride Solution, Mild
Naphazoline Hydrochloride Solution, Strong
Nicotinamide Capsules
Nicotinic Acid Capsules
Nikethamide (Coramine)
Nikethamide Injection
Nitrogen
Ox Bile Extract Capsules
Oxytocin Injection (Pitocin)
Para-aminobenzoic Acid
Para-aminobenzoic Acid Tablets
Paraffin
Penicillin G Potassium (Crystalline)
Penicillin G Sodium (Crystalline)
Penicillin Buffered Crystalline
Penicillin for Inhalation
Penicillin, Procaine
Penicillin, Procaine for Aqueous Injection
Penicillin, Procaine, Oil Injection
Pentaquine Phosphate
Pentaquine Phosphate Tablets
Pentobarbital Sodium Injection
Pentobarbital Sodium, Sterile
Pentylenetetrazol (Metrazol)
Pentylenetetrazol Injection
Pertussis Vaccine
Pertussis Vaccine, Alum Precipitated
Phenobarbital Sodium Injection
Phenobarbital Sodium, Sterile
Phenylephrine Hydrochloride (Neo-Synephrine HCl)
Phenylephrine Hydrochloride Injection
Phenylephrine Hydrochloride Solution
Phthalylsulfathiazole (Sulfathalidine)
Phthalylsulfathiazole Tablets
Pilocarpine Hydrochloride
Piperocaine Hydrochloride (Metycaine Hydrochloride)
Piperocaine Hydrochloride Injection
Polyethylene Glycol 400
Polyethylene Glycol 4000 (Carbowax 4000)
Polyethylene Glycol 400 Monostearate
Polyethylene Glycol Ointment
Polysorbate 80 (Tween 80)
Potassium Nitrate
Procaine Hydrochloride Injection
Procaine Hydrochloride and Epinephrine Injection
Procaine Hydrochloride, Sterile
Progesterone Injection
Propylene Glycol
Propylthiouracil
Propylthiouracil Tablets
Protein Hydrolysate Injection
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Quinine Sulfate Capsules
Raspberry Juice
Raspberry Syrup
Rose Water Ointment, Petrolatum
Salicylic Acid Plaster
Scopolamine Hydrobromide Tablets
Serum, Anti-A Blood Grouping
Serum, Anti-B Blood Grouping
Serum, Anti Rh Typing
Silver Nitrate Ophthalmic Solution
Sodium Bicarbonate Tablets
Sodium Bisulfite
Sodium Iodomethamate (Neo-Iopax)
Sodium Iodomethamate Injection
Sodium Salicylate Injection
Sponge, Absorbable Gelatin
Stibophen
Stibophen Injection
Streptomycin
Sulfadiazine Sodium Injection

Sulfamerazine Sodium Injection
Sulfathiazole Sodium Injection
Sulfur Dioxide
Suprarenal Cortex Injection
Suramin Sodium Sterile
Testosterone
Testosterone Pellets
Testosterone Proprionate Injection
Theobromine Calcium Salicylate (Theocalcin)
Theobromine Calcium Salicylate Tablets
Thrombin
Trimethadione (Tridione)
Trimethadione Capsules
Trimethadione Tablets
Tripelennamine Hydrochloride (Pyribenzamine Hydrochloride)
Tripelennamine Hydrochloride Tablets
Tubocurarine Chloride
Tubocurarine Chloride Injection
Tyrothricin
Tyrothricin Solution
Tyrothricin Spray
Tyrothricin Troches
Vanilla
Vanilla Tincture
Vasopressin Injection (Pitressin Injection)
Vassopressin Tannate Injection
Zinc Gelatin
Zinc Oxide Paste

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Alum
Alum, Exsiccated
Anise Water
Arsenic Trioxide
Arsphenamine
Belladonna Ointment
Benzyl Benzoate, Saponated
Betanaphthol
Boroglycerin Glycerite
Butyl Aminobenzoate
Caffeine, Citrated
Calcium Iodobehenate
Camphor and Soap Liniment
Cedar Leaf Oil
Chalk Mixture
Chalk, Prepared
Charcoal, Activated
Chloroform Liniment
Cholera Vaccine
Chromium Trioxide
Cinnamon Spirit
Clove
Cod Liver Oil Emulsion
Cresol Solution, Saponated
Cupric Citrate
Cupric Citrate Ointment
Effervescent Powders, Compound
Ethyl Aminobenzoate Ointment
Eucalyptus Oil
Fennel Water
Formaldehyde Solution
Gas Gangrene Antitoxin, Bivalent
Gas Gangrene Antitoxin, Pentavalent
Gas Gangrene Antitoxin, Trivalent
Ginger
Ginger Fluidextract
Hyoscyamus
Hyoscyamus Tincture
Lard
Lard, Benzoinated
Lavender Spirit
Lavender Tincture, Compound
Lead Acetate
Mercurial Ointment, Mild
Mercurial Ointment, Strong
Mercurous Chloride, Mild
Mercury
Mercury Oleate
Methylene Blue
Methylrosaniline Chloride
Mustard, Black
Mustard Plaster
Myristica
Myrrh
Myrrh Tincture
Neoarsphenamine

Orange Flower Syrup
Orange Peel, Bitter, Tincture
Penicillin Dental Cones
Penicillin Injection in Oil and Wax
Penicillin Sodium (Replaced by Penicillin G. Sodium)
Petrolatum, Liquid, Light
Phenacaine Hydrochloride
Phenol Ointment
Plague Vaccine
Potassium Acetate
Potassium Arsenite Solution
Potassium Carbonate
Potassium Citrate
Potassium Citrate, Effervescent
Potassium Sodium Tartrate
Quinine Bisulfate
Red Saunders
Rhubarb, Aromatic, Syrup
Rhubarb, Aromatic, Tincture
Scarlet Fever Streptococcus Antitoxin
Scarlet Fever Streptococcus Toxin
Senna
Senna, Fluidextract
Senna Syrup
Serum, Normal Human
Silver Nitrate, Toughened
Silver Protein, Mild
Soap, Hard
Soap, Soft, Liniment
Sodium Carbonate, Monohydrated
Sodium Hydroxide
Sodium Hypochlorite Solution
Sodium Perborate
Sodium Sulfite, Exsiccated
Sodium Thiosulfate
Spearmint
Spearmint Spirit
Spearmint Water
Stearic Acid
Stramonium
Stramonium Extract
Stramonium Tincture
Strychnine Sulfate
Strychnine Sulfate Tablets
Sulfarsphenamine
Sulfur, Sublimed
Tannic Acid
Tannic Acid Glycerite
Tannic Acid Ointment
Tar, Juniper
Tar, Pine
Tar, Pine, Ointment
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Theopylline Tablets
Thymol
Thyroxin
Totaquine
Totaquine Capsules
Totaquine Tablets
Tragacanth Mucilage

SELECTED ABSTRACTS

Identification of Sulfonamides in Mixtures. E. Hucknall and G. E. Turfitt. *J. Pharm. Pharmacol 1*:368 (1949). From an analytical standpoint no reaction specific for the typical sulfonamide linkage has been developed. Most reactions are based upon some chemical reaction involving the free primary amino group. While such reactions are satisfactory under some conditions they are valueless with sulfonamides in which the primary amino group is substituted. The authors attempted to develop a simple technique for the identification of the drugs in micro-quantities.

The procedure developed by the authors involves the preliminary purification of crude residues by heating with activated charcoal in acetone. A preliminary melting point is then taken. Provisional identification as a sulfonamide is then accomplished by fusing with soda-lime. The products thus obtained are ammonia or readily volatile amines, aniline bases, and sodium sulfite or sulfide. A simple test for the primary amino grouping is condensation with furfural in acetic acid. As the liquid evaporates an intense red color develops. The next step is the formation of crystals. On a glass slide 0.1 mg. of the drug is dissolved in 1 drop of ammonia solution. A drop of glacial acetic acid is then held above the slide until turbidity appears around the margin of the drop. The crystals are then examined under a microscope. The crystals thus formed are usually very distinctive and it is often possible to identify a sulfonamide by this test alone. A confirmatory test performed by warming the drug with vanillin and concentrated sulfuric acid is recommended by the authors. Most of the sulfonamides give a yellowish-green color but sulfamerazine and sulfadimidine give an intense bright red color. The final confirmation of the identification of the sulfonamide is the running of a mixed melting point with a sample of the indicated compound.

When mixtures of the sulfonamides are involved a preliminary separation of the components is necessary. This can be accomplished satisfactorily on the basis of solubility difference using a prescribed list of common solvents.

Aureomycin in the Therapy of Syphilis. P. A. O'Leary, R. R. Kierland, and W. E. Herrell. *Proc. Staff Meet. Mayo Clin. 24*:302 (1949). According to the results reported by the authors in the treatment of two cases of syphilis of long standing aureomycin shows promise as a therapeutic agent in the treatment of this disease. One patient was given the antibiotic orally every six hours on the following schedule: 250 mg. for 3 days, then 500 mg. for 3 days, then 750 mg. for 2 days, and then 1 Gm. until a total of 56:5 Gm. of aureomycin had been given over a period of 18 days. By the fifth day of treatment improvement could be observed in the lesions and when the patient returned for observation at the end of 69 days the lesions were completely healed. However, the serologic tests for syphilis were still positive.

The second patient was given 250 mg. every 6 hours for 2 days. At this time there was marked improvement in the lesions. Therapy was then increased to 1 Gm. every 6 hours. This increase was tolerated for 5 days but then nausea and vomiting developed. Consequently the dose was reduced to 500 mg. every six hours and maintained at this level until a total of 60 Gm. of aureomycin were given. No further side reactions were encountered. The lesions healed rapidly in this case also.

The authors suggested that aureomycin may fill a need for an antibiotic which may be effectively used in place of penicillin in those patients showing resistance to or sensitivity to penicillin.

Therapy of Endocrine and Gynecic Disorders With Pellets Implantation. R. B. Greenblatt and R. R. Suran. *Am. J. Obst. Gynecol. 57*:294 (1949). The implantation of hard compressed pellets of crystalline hormones has been shown to give a slow absorption of the hormone more closely resembling natural secretion than can be obtained by parenteral injection. The amount of hormone released to the body is small but continuous. Pellet implantation also eliminates the inconvenience of frequent injections in conditions requiring prolonged therapy. A single implantation may give therapeutic results for periods up to 6 months or even longer.

The sterile pellets are inserted through a hollow needle into the subcutaneous tissue. The site chosen is usually on the anterior abdominal wall about one inch medial to the anterior superior spine of the iliac crest, on either side. As many as 12 pellets have been implanted at one injection. A dry dressing is applied following the implantation. The authors stated that extrusion of the pellets occurred in less than 2 per cent of the cases.

The rate of absorption of the hormone depends on the number of pellets implanted at one time and not on the size or weight of the pellets. However, the length of time that the pellets continue to give off appreciable amounts of the hormone depends on the size and weight of the pellets implanted. The rate of absorption is relatively rapid during the first month and then decreases until it tends to level off after about 3 months.

A list of indications for the use of hormone pellets is given by the authors. The basic indication is for those conditions where prolonged therapy appears to be necessary. Several case histories are also given in which a variety of endocrine and gynecic disorders were treated with good results. Pellets of estradiol, progesterone, testosterone, and desoxycorticosterone were used.

New Human Agglutinogen of High Population Incidence Named Cellano. P. Levine, M. Wigod, and R. Ponder. *Science 109*:464 (1949). An immune agglutinin obtained from the blood of the mother of an infant with a mild form of hemolytic disease has indicated the presence of a new agglutinogen in human blood. This new factor is unusual in the fact that it is present in such a high incidence. The agglutinogen was found to be present in 99.8 per cent of 2500 blood specimens tested with the agglutinin. The factor has been named "Cellano" for the patient in whom it was first found, and its antibody has been named "anti-Cellano."

The authors reported that a study was made of the antigenic structure of the parents and the brothers and sisters of one of the patients found to be lacking the Cellano factor. They found that this new factor is independent of the AB, MN, and Rh-Hr systems. It

was found that both the parents were positive reactors but were heterozygous for, 3 of the 8 children tested were Cellano negative.

From these studies it was calculated that the genetic homologue of the Cellano factor would be present in 8.8 per cent of the population of which 0.2 per cent would be homozygous and 8.6 per cent would be heterozygous. Another human anti-body, Kell, was tested in the above mentioned family. It was found that both parents were also heterozygous as to Kell and that 6 of the 8 children were Kell positive. Parallel tests with anti-Cellano and anti-Kell serums in this family showed that the genes for Cellano and Kell antigens are alleles.

The Combined Action of Various Antibiotics and Sulfonamides. C. W. Price, W. A. Randall, H. Welch, and V. L. Chandler. *Am. J. Pub. Health 39:*340 (1949). The authors performed a study to determine the chemotherapeutic action of various mixtures containing penicillin, streptomcyin, polymyxin, bacitracin, aureomycin, chloromycetin, sulfathiazole, sulfadiazine, and sulfamerazine. Tests were performed *in vitro* and *in vivo* using as the test organism *Salmonella typhosa.* As a preliminary step each antibiotic or sulfonamide was tested over a wide range of concentrations to determine its individual effects on the test organism. The various combinations were then prepared using the concentration which had a slight but definite protective or inhibitive effect when the drug was used alone, both *in vitro* and *in vivo.*

The results obtained indicated that where synergism was shown between two of the chemotherapeutic agents the range of concentration showing such synergism was quite narrow. In some cases additive effects were shown while in others antagonistic effects were obtained. The results also showed that certain drug combinations gave markedly different results with the two test methods employed. One case showed the extreme of synergism *in vitro* and antagonism *in vivo.* Thus this study has shown that *in vitro* test results cannot be taken as a definite indication of clinical results to be expected.

Of the combinations tested *in vitro* polymyxin showed a synergistic effect with aureomycin, bacitracin, penicillin, and streptomycin;

penicillin showed synergism with aureomycin and streptomycin; and streptomycin showed a similar effect with sulfathiazole and sulfadiazine. Combinations *in vivo* showed that penicillin was synergistic with streptomcyin, sulfadiazine, aureomycin, sulfamerazine, and sulfathiazole; streptomycin showed a similar effect with sulfadiazine, sulfathiazole, and sulfamerazine; and chloromycetin with sulfamerazine and sulfathiazole. Among these combinations showing a synergistic effect only about 50 per cent of the cases showed a correlation between the two test methods.

Daily Requirements of Vitamin A. Medical Research Council Report. *Pharm. J.* 162:452 (1949). A study was conducted to determine the minimum daily requirements for vitamin A in the normal healthy adult. A group of 23 volunteers were placed on a diet of natural foodstuffs essentially free of vitamin A and of carotene, but otherwise dietarily complete. This diet was consumed for a period varying from ½ to 25 months. Seven of the subjects served as controls and 5 were given 5000 I. U. of β-carotene and 2 received 2500 I. U. of vitamin A a day.

The vitamin A and the carotene levels in the blood of each subject were determined at frequent intervals and the faeces were tested for total carotenoids and for α—and β-carotene. The capacity for dark adaptation was estimated by means of the adaptometers of Wald and Craik and later by the rod scotometry method of Livingstone. The blood level determinations and the dark adaptation were the only tests which were of any value in determining depletion and even these varied considerably. Very little difference could be detected clinically between the treated and the untreated subjects.

The blood levels of total carotenoids were reduced by 50 per cent within the first month. A slightly lower level was reached and then fairly uniformly maintained for about 2 years. The vitamin A level behaved differently. No indication of lowering was obtained for about 8 months and then only 10 of the 16 subjects showed a pronounced lowering. As the vitamin A blood level decreased there was a definite deterioration in dark adaption.

Although depletion was not complete in most of the patients, treatment with 1250 I. U. of carotene in oil or of 1300 I. U. of vitamin A a day was instituted. Slow improvement occurred with more rapid improvement with 2500 I. U. of vitamin A a day. This latter dose also seemed to adequately maintain the 2 control subjects receiving vitamin A. It was found that there was less loss of carotene by excretion when it was given in oil rather than in the natural form of carrots or cabbage.

The report concluded that a normal person has a considerable reserve of vitamin A which is not readily depleted. It also concluded that a minimum daily intake of 2500 I. U. of vitamin A or 7500 I. U. of β-carotene would allow a good margin of safety.

BOOK REVIEWS

Absorption Spectrophotometry. By G. F. Lothian, M.A., F. Inst. P. Third Edition. 196 pages, 71 figures. Hilger and Watts Ltd., London. Price: 26 shillings.

This new and renamed edition of *The Practice of Absorption Spectrophotometry with Hilger Instruments* represents an extensive revision and rewriting of its predecessor volume. The book is divided into three divisions dealing, respectively, with general principles, typical applications, and techniques of spectrophotometric methods. Measurements in the untraviolet, visible and infrared regions of the spectrum by photographic, visual and photoelectric methods are discussed. While "representative instruments" are described, the Hilger instruments are treated more fully.

The book should be of special interest to those desiring an introduction to spectrophotometric methods, as well as to those who have had too much experience with such procedures.

ARTHUR OSOL

Outlines of Biochemistry. By Ross Aiken Gortner. Third Edition, 1078 pages incl. index; edited by Ross Aiken Gortner, Jr. and Willis Alway Gortner. John Wiley & Sons, Inc., New York; 1943. Price: $7.50.

This the third edition of one of the best known texts on biochemistry is a much needed revision of the second edition which was published over ten years ago. The revision of the text was accomplished by the contributions of ten outstanding biochemists most of whom were one-time students of the late Dr. Gortner. Dr. Gortner's two sons, both themselves biochemists of note, edited the third edition and in such a fashion that the standard of excellence set by their father is maintained.

A considerable amount of revision in the text has been accomplished. The section on colloids has been reduced in order to devote more space to new chapters on protein denaturation, carbohydrate metabolism and lipid metabolism. The chapters on protein metabolism, the vitamins and the polysaccharides have been expanded and brought up to date while others have been condensed or deleted with their contents combined with other chapters. The book is divided in six sections, namely: Colloids, Proteins, Carbohydrates and Related Substances, The Lipids and Essential Oils, Plant Pigments and Biochemical Regulations.

The style and contents are those of a general text on biochemistry without special emphasis being placed on agricultural or medical aspects. For this reason the text has a broad appeal and utility. The printing and binding are excellent and the book for its contents seems to be priced most moderately.

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